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Review Article

Recent advancements in oxadiazole-based anticancer agents

Irfan Rasool[1], Matloob Ahmad[1]*, Zulfiqar Ali Khan[1], Asim Mansha[1], Tahir Maqbool[1], Ameer Fawad Zahoor[1] and Sana Aslam[2]*

[1]Department of Chemistry, Government College University, Faisalabad-38000, Pakistan, [2]Department of Chemistry, Government College Women University, Faisalabad-38000, Pakistan

For correspondence: **Email: Matloob.Ahmad@gcuf.edu.pk, matloob_123@yahoo.com, sana_gy@yahoo.com; **Tel:** 0092-41-2649975*

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Abstract

Oxadiazole ring system occupies a significant position among heterocyclic templates for medicinal compounds due to its wide spectrum of biological activities. This article entails an in-depth review of the ability of oxadiazole derivatives to induce apoptosis of cancer cells. FDA has approved a number of drugs for the treatment of different types of cancer. There is, however, a continuing need for the development of new anticancer agents due to increasing cases of drug resistance. Moreover, medicinal chemists are continuously struggling to invent selective cytotoxic agents with minimum side effects. This work reviews the significance of oxadiazole ring system and its potential to act as a template for novel anticancer agents.

Keywords: *Oxadiazole ring system, Anticancer activity, Antitumor activity, Cytotoxicity, Apoptosis*

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INTRODUCTION

Cancer is a continued threat for humanity on the globe both in advanced countries as well as developing ones. Various anticancer drugs have been approved by FDA for the treatment of different types of cancers. Most of them are structurally based upon heterocyclic ring systems. Oxadiazole ring system is at significant position among heterocycles due its medicinal properties. This ring system exists in the form of structural isomers 1,3,4-oxadiazole, 1,2,4-oxadiazole and 1,2,3-oxadiazole.

1,3,4-Oxadiazole

1,3,4-Oxadiazole derivatives are frequently reported for their anticancer activity. A series of 1-[{(5-Alkenyl/hydroxyalkenylsubstituted)-1,3,4-oxadiazol-2-yl}-methyl]-2-methyl-1*H*-benzimidazoles has been recently reported as anticancer agents. Among them, compounds **1, 2** & **3** showed moderate to weak activity against Hep3B (human hepatocellular carcinoma), HeLa (human cervical carcinoma) and MCF 7 (human breast adenocarcinoma) cell lines (Table **1**) [1]. A series of indole and 1,3,4-oxadiazole hybrid compounds were recently prepared by Hatti and coworkers and were screened against MCF-7, KB, Colo-205, and A-549 cancer cell lines. Among them, compounds **4-8** were found to exhibit significantly higher anticancer activity as compared to the reference drug etoposide (Table **2**) [2]. Rashid *et al* prepared 3-((5-(3-(1*H*-benzo[*d*]imidazol-2-yl)-3-oxopropyl)-1,3,4-oxadiazol-2-yl)methyl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (**9**) which exhibited significant

antiproliferative activity with GI_{50} value of 0.09 µM [3].

Yonova *et al* reported 2-phenyl-5-(phenylthio)-1,3,4-oxadiazole (**10**) as selective anticancer agent against the MCF-7 with EC_{50} value of 7.9 µM [4]. Valente *et al* described the synthesis of hydroxamates and 2-aminoanilides having 1,3,4-oxadiazole moiety as histone deacetylase inhibitors. Among the series of naphthalene based oxadazoles, compounds **11** and **12** appeared as the most potent and selective compounds against HDAC1. Compound **11** was more effective against U937 leukemia cells with IC_{50} value of 7.8 µM than reference drug (SAHA) and compound **12** displayed cell di□erentiation comparable to reference, MS-275 [5]. Kumar *et al* synthesized oxadiazole containing sulfonamides **13** and **14** which were weakly active against K562, Colo-205, MDA-MB231 and IMR-32 cancer cell lines as shown in the Table **3** [6].

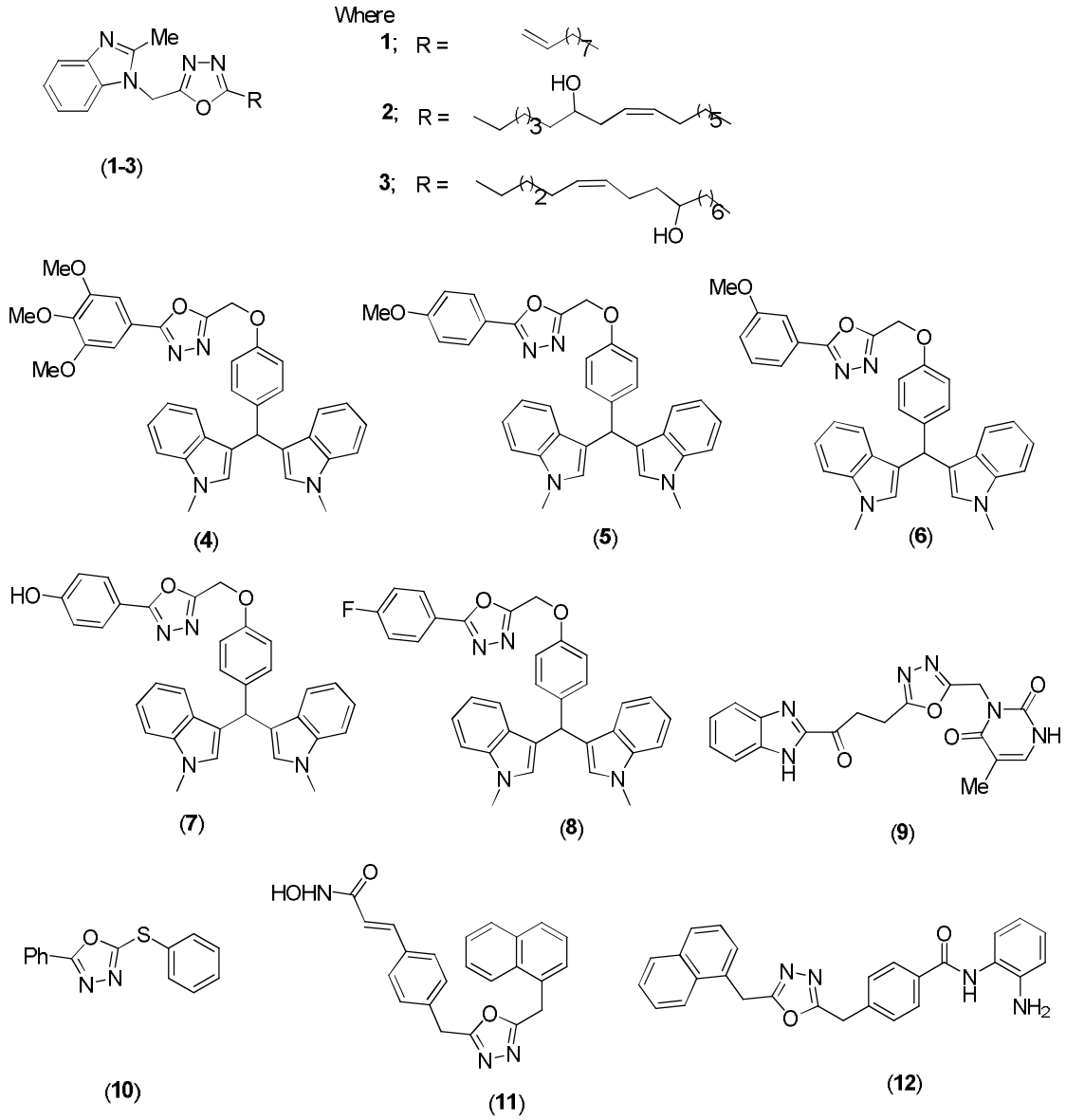

Figure 1: Structures of 1,3,4-Oxadiazoles (1-12) exhibiting potent anticancer activity

Table 1: IC_{50} (µM) values of compounds **1 - 3** against various cancer cell lines

Compound	Hep3 B	MCF 7	HeLa	PBMC
1	11.10 ± 1.1	12.40 ± 0.5	11.70 ± 2.9	42.42 ± 1.2
2	14.10 ± 0.8	12.20 ± 0.7	14.40 ± 1.2	41.27 ± 1.8
3	13.90 ± 0.8	11.10 ± 0.7	10.60 ± 1.2	43.28 ± 1.8
Doxo	02.35 ± 1.2	03.12 ± 1.7	03.56 ± 2.7	09.23 ± 2.6
5-Fu	03.45 ± 2.1	04.12 ± 2.3	02.78 ± 2.6	08.91 ± 1.9

Table 2: Cytotoxic activity (GI_{50}/µM) of compounds **4 – 8**

Compound	Breast MCF-7	Oral KB	Colon Colo-205	Lung A-549
4	<0.1	<0.1	1.3	<0.1
5	0.12	–	0.13	<0.1
6	0.14	<0.1	<0.1	<0.1
7	<0.1	0.11	–	<0.1
8	<0.1	0.18	0.15	<0.1
Etoposide	2.11	0.31	0.13	3.08

Table 3: Anti-proliferative activity (% cell survival) of compounds **13** and **14** (10 µM)

Compound	K562	Colo-205	MDA-MB 231	IMR-32
13	59.31	64.00	62.40	68.22
14	48.20	61.70	60.05	60.81
Control (0.1 % DMSO)	100	100	100	100

Zhang *et al* reported the synthesis of structural hybrids of 1,3,4-oxadiazole and 1,3,4-thiadiazole heterocycles having schiff base side chain. Among these compounds, compound **15** exhibited growth inhibition of SMMC-7721 cells with IC_{50} value of 2.84 µM. Compounds **16** and **17** displayed antitumor activity with IC_{50} values of 4.56 and 4.25 µM, respectively against MCF-7 cells. Compounds **17** and **18** exhibited significant anti-proliferative activity against A549 cells, with IC_{50} values of 4.13 and 4.11 µM, respectively [7].

Quinoline substituted 1,3,4-oxadiazoles are reported for their inhibitory potential against HepG2, SGC-7901 and MCF-7 cell lines. Among the series, compounds **19** and **20** showed the best activity among the series and the results were comparable to the control as shown in table **4** [8]. Murty *et al* coupled piperazine substituted benzothiazole/benzoxazole with 1,3,4-oxadiazole-2-thiol to get corresponding structural hybrids **21** and **22** which displayed excellent cytotoxic activity as shown in the Table 5 [9].

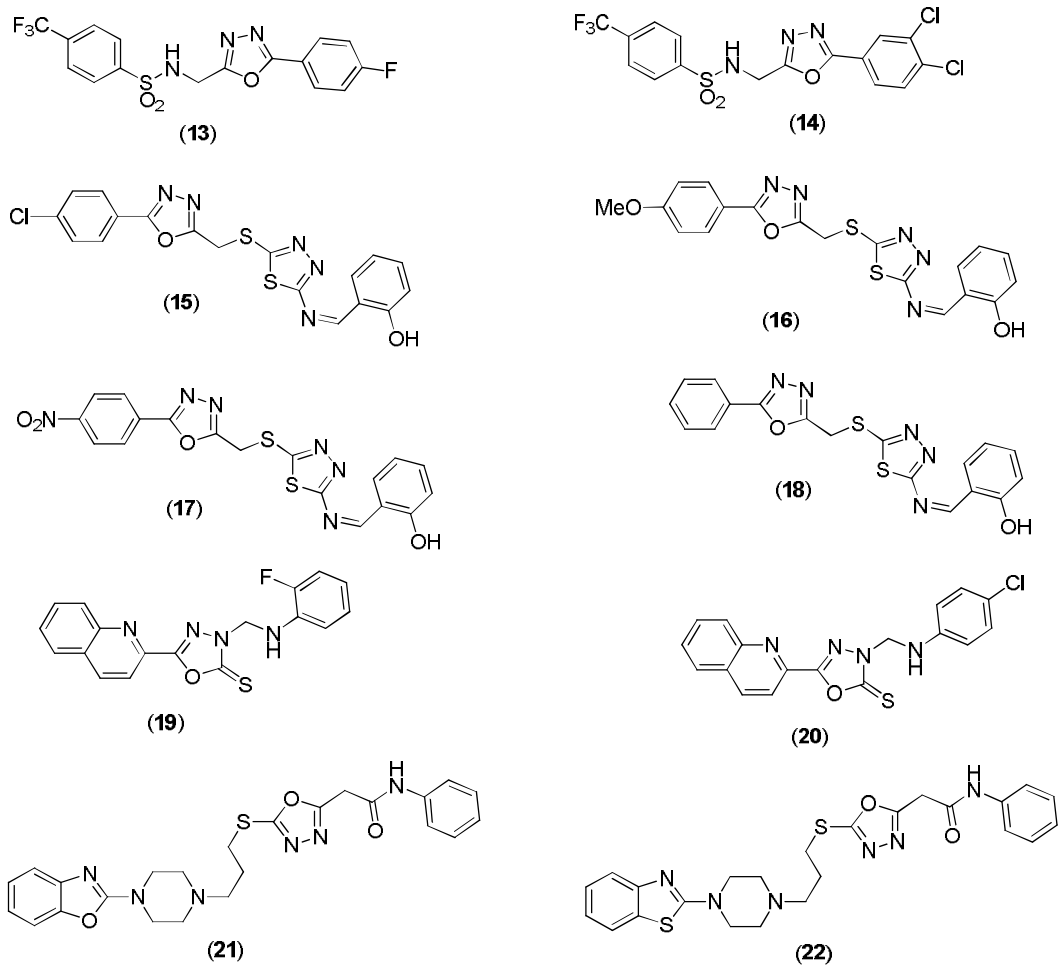

Figure 2: Structures of 1,3,4-Oxadiazoles (**13-22**) exhibiting potent anticancer activity

1,3,4-Oxadiazoles derivatives (**23** and **24**) exhibited good activity with IC_{50} values of 16 µM and 10 µM respectively against K562 cancer cell line [10]. Shamsuzzaman *et al* synthesized **25** that exhibited moderate anticancer behavior against human leukemia cell line (HL-60) (IC_{50} =17.33) [11].

Bondock *et al* synthesized heterocyclic 1,3,4-oxadiazole derivatives derivatives (**25**-**30**) that displayed promising in-vitro antitumor activity as shown in the Table **6** [12]**.** Feng *et al* synthesized a series of thio-substituted 1,3,4-oxadiazole derivatives (**31** & **32**) and screened them against human leukemia tumor cell line (K-562). Compounds **31** and **32** were docked into the ATPase domain of TP-II and docking scores are shown in the Table 7 [13].

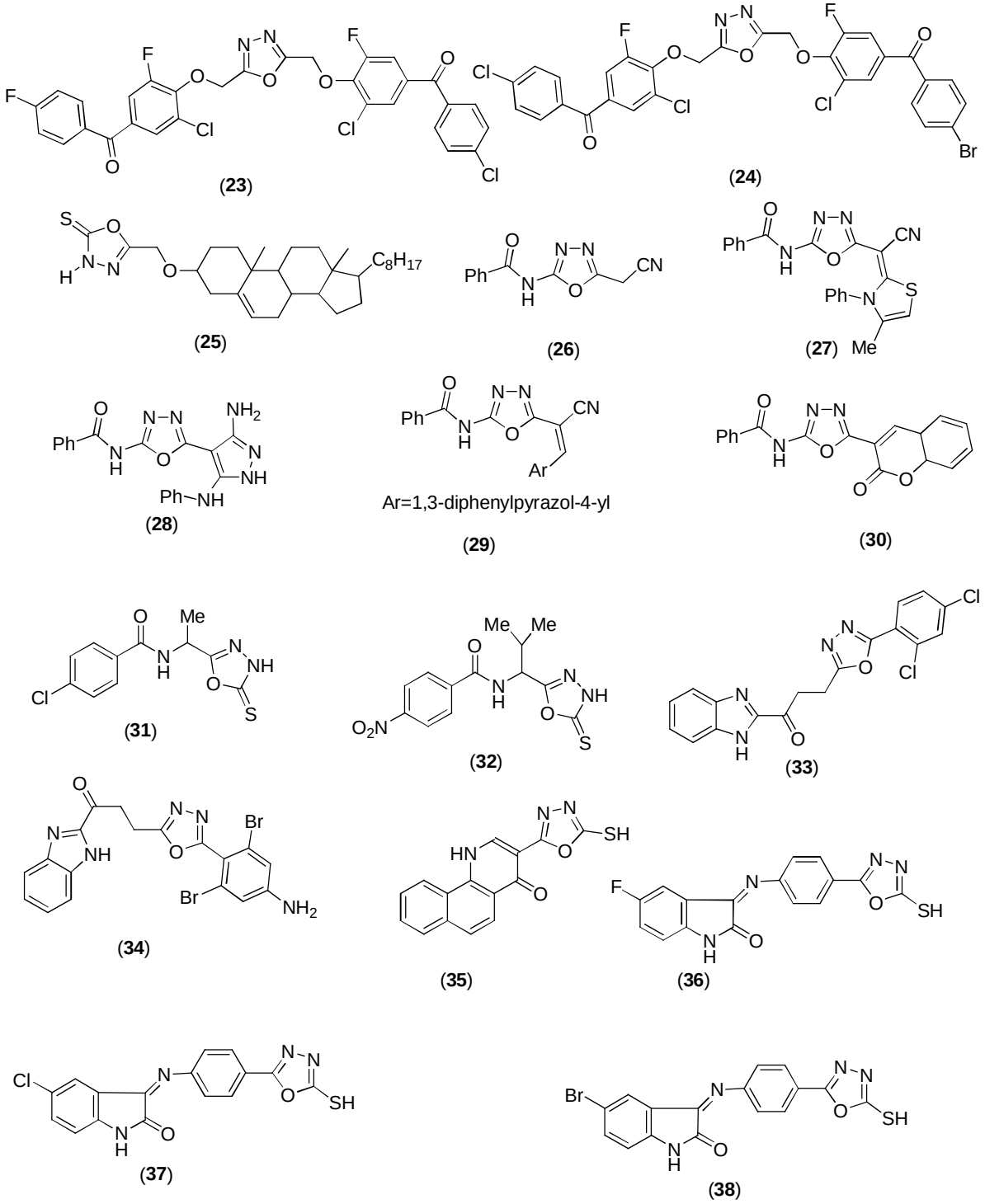

Figure 3: Structures of 1,3,4-Oxadiazoles (23-38) exhibiting potent anticancer activity

Table 4: Anticancer activities (IC_{50}, µM) of compounds **19** and **20**

Compound	HepG2	SGC-7901	MCF-7
19	1.2±0.2	8.3±1.6	6.8±0.5
20	0.8±0.2	7.6±1.0	7.1±0.8

Table 5: Cytotoxic activity (IC_{50}, µM) of compounds **21** and **22**

Compound	MCF 7	HeLa	A431	HepG2	A549
21	52.7	63.9	36.9	88.9	102.0
22	39.0	78.1	55.9	325.1	88.7
Curcumin	26.0	17.0	22.0	16.0	22.0

Table 6: Cytotoxicity values [IC_{50} (µg/ml)] of compounds **26 – 30**

Compound	HepG2	WI-38	VERO	MCF-7
26	21.2	24.4	30.3	39.2
27	12.4	17.3	15.8	25.8
28	33.7	38.4	36.3	38.3
29	38.1	24.1	39.6	37.4
30	35.6	35.8	34.5	32.6
5-Fu	8.6	3.2	6.5	2.3

Table 7: Docking score and IC_{50} values for compounds **31** and **32**

Compound	Glide {TP-II (PDB: 1ZXM)}	Glide {Tubulin (PDB: 1SA0)}	K562 [IC_{50} (µM)]
31	>-5	>-5	31.14
32	-6.87	>-5	43.55
Hydroxy-urea (standard drug)	-	-	687.94

Benzimidazole and oxadiazole hybrids were synthesized by Rashid *et al.* Amongst them, compound **33** emerged as the most significant anticancer agent against various cancer cell lines [14]. Husain *et al* also synthesized benzimidazole and oxadiazole hybrids. Among them, compound **34** exhibited significant growth inhibition [15]. Fadda *et al* synthesized a new series of quinoline based oxadiazoles. The compound **35** showed a strong cytotoxicity as shown in the Table **8** [16].

Gudipati *et al* synthesized a series of indole containing oxadiazoles. The compounds produced a dose dependent inhibition of the growth of HeLa cancer cell line. The IC_{50} values were found between 10.64 and 33.62 µM. The compounds **36, 37 & 38** exhibited anticancer activity comparable to Cisplatin (Table 9) [17].

Dash *et al* synthesized the series of 3,5-disubstituted 1,3,4-oxa-diazole-2-thione derivatives. Among the synthesized compounds, the compounds **39, 40, 41, 42 & 43** were found more active than 5-FU as shown in Table 10 [18]. Zhang *et al* synthesized 1,4-benzodioxane based 1,3,4-oxadiazoles as potential telomerase inhibitors. Compounds **44, 45, 46, 47** and **48** were observed as potent anticancer compounds with IC_{50} concentration range from 7.21 µM to 25.87 µM against HEPG2, SW1116, HELA and BGC823 [19].

Abu-Zaied *et al* synthesized novel thioglycosides having 1,3,4-oxadiazole moiety. The pharmacological evaluation of compounds **49, 50** and **51** was carried out and the compounds were found to be effective against MCF-7 (breast) and HEPG2 (liver) cells. The IC_{50} values were found in the range of 2.67-20.25 (µg/mL) for MCF-7 (breast cancer cell line) and 4.62-43.6 (µg/mL) for HEPG2 (liver cancer cell line) [20].

5-(3-Indolyl)-2-(substituted)-1,3,4-oxadiazoles were screened for human cancer cell lines and among the compounds, compounds **52, 53** and **54** exhibited potent cytotoxicity (IC_{50}~1 µM) and selectivity against human cancer cell lines as shown in Table **11** [21]. Tong *et al.* described the synthesis of compound **55** showed the best activity with EC_{50} value of 3.7 µM [22]. Oxadiazole compounds **56** and **57** were appeared as potent members of anticancer family of drugs [23].

1,2,4-Oxadiazole

There are sufficient number of evidence dealing with anticancer behavious of 1,2,4-oxadiazole derivatives. 5-(5,7-Dimethylpyrazolo[1,5-a]pyrimidin-3-yl)-3-(piperazin-1-ylmethyl)-1,2,4-oxadiazole based carboxamides, sulfonamides, ureas, and thioureas are recently reported for

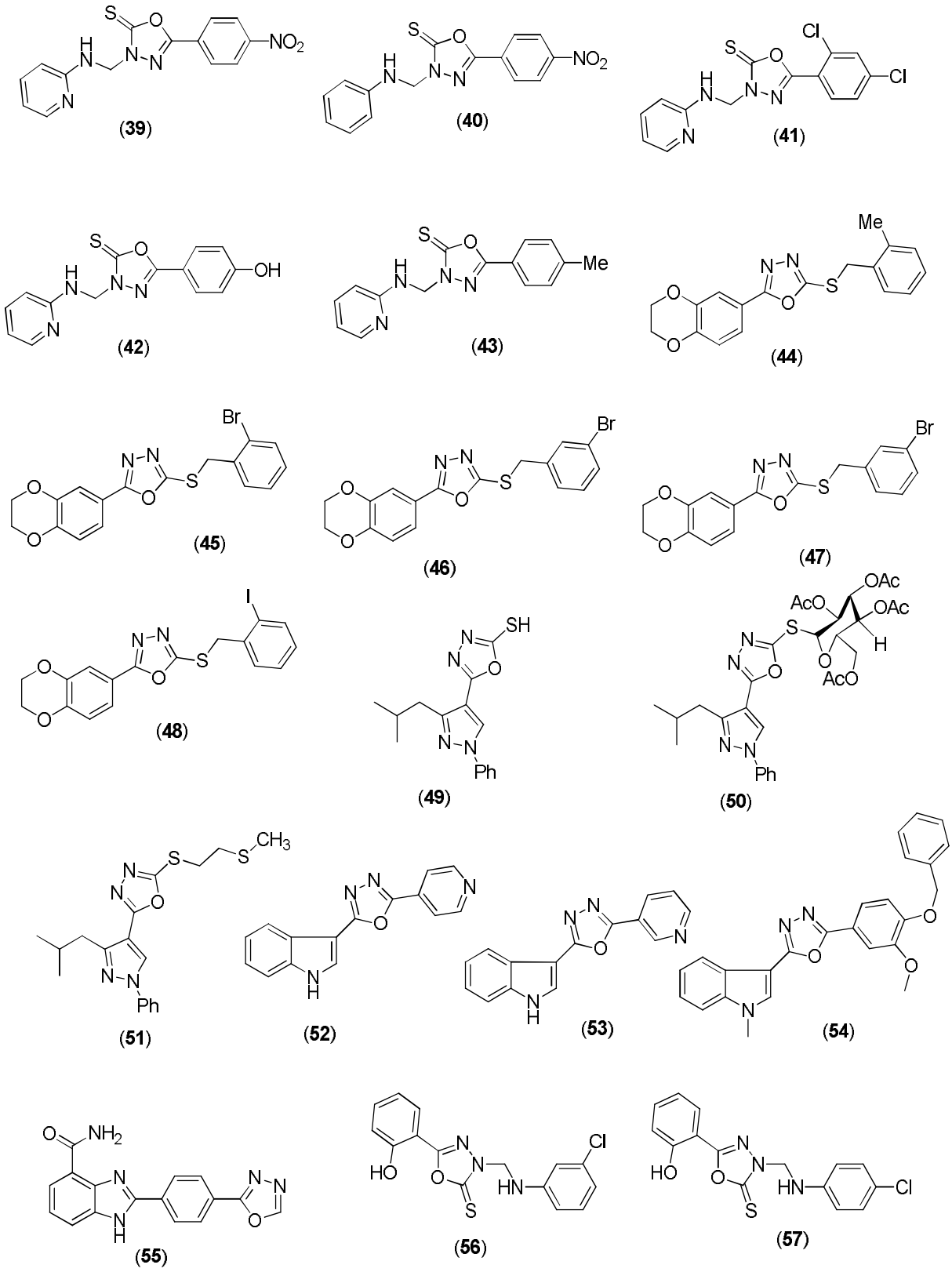

Figure 4: Structures of anticancer 1,3,4-Oxadiazoles (**39-57**)

Table 8: Cytotoxicity of the Synthesized Compound **35** (IC_{50}, µg/ml)

Compound	HepG2	WI-38	VERO	MCF-7
35	22.4	27.3	25.8	40.8
5-Fluorouracil	8.6	3.2	6.5	2.3

Table 9: Cytotoxicity of the Synthesized Compounds **36-38** (IC_{50}, µg/ml)

Compound	IC_{50} (µM, HeLa)	IC_{50} (µM, IMR-32)	IC_{50} (µM, MCF-7)
36	11.99	13.48	15.57
37	12.84	15.84	16.68
38	10.64	12.68	16.06
Cisplatin	14.08	13.64	13.54

Table 10: Anticancer activity of oxadiazole derivatives against EAC bearing mice

Compound	RBC (106 cells)	WBC (103 cells)
Normal saline	11.04 ± 0.33	4.47 ± 0.15
Induce control	2.77 ± 0.13	10.31 ± 0.23
39	3.57 ± 0.20*	7.73 ± 0.21***
40	5.68 ± 0.30***	5.57 ± 0.14***
41	7.23 ± 0.07***	4.47 ± 0.12***
42	6.25 ± 0.16***	4.97 ± 0.10***
43	8.27 ± 0.16***	4.62 ± 0.14***
5-Fluorouracil	8.32 ± 0.15***	4.81 ± 0.14***

*Test compounds were compared with induce control; * $p < 0.05$, *** $p < 0.01$*

Table 11: Cytotoxicity (IC_{50}, µM) of 5-(3-indolyl)-2-(substituted)-1,3,4-oxadiazoles (**52 - 54**)

Compound	PC3	DU145	LnCaP	MDA-MB-231	MCF7	PaCa2
52	4.1	20.4	10.0	$>10^3$	1.0	1.6
53	710.8	170	69.4	$>10^3$	5.4	0.9
54	$>10^3$	$>10^3$	$>10^3$	$>10^3$	35.2	1.4

their effective activity against HeLa cells. Five compounds **58-62** exhibited activity with IC_{50} value <10 µg/cm^3 which was greater than reference drug, paclitaxel with IC_{50} value 30 µg/cm^3 [24]. Miralinaghi *et al* described the synthesis of triaryl-1,2,4-oxadiazole derivatives and screened them for anti-proliferative activities against MCF7 and K562 cell lines using MTT assay. Out of these, compound **63** showed remarkable activity against MCF7 and K562 cell lines with IC_{50} values of 6.50 and 21.66 µM, respectively [25].

Tsygankova and Zhenodarova reported a series of 3,5-Diaryl-1,2,4-oxadiazoles derivatives. Five compounds **(64-68)** were found more active against antitumor agents as shown in the table **12** [26]. 1,2,4-Oxadiazole (**69**) exhibited effective activity against DU145 (IC_{50} : 9.3 µM) cell lines [27].

Previously, Yang *et al* synthesized the series of Oxadiazole derivatives as inhibitors of human leukemia HL-60 cells. Compound **70** was one of the potent anti-proliferative agent without inhibition of GST P1-1 activity. Compounds **71** and **72** exhibited antitumor activity with IC_{50} value less than 5 µM as shown in the table **13** [28]. Kemnitzer *et al* synthesized a new series of 3-aryl-5-aryl-1,2,4-oxadiazoles. Compound **73** was found more active against T47D cancer cell growth with GI_{50} value of 0.13µM [29]. Kumar *et al* synthesized a series of 3,5-disubstituted-1,2,4-oxadiazoles. Compound **74** appeared as the most selective (>450-fold) whereas **75** as the most potent compound having IC_{50} value of 10 nM against prostate cancer cell lines (Table 14) [30].

Thiophene containing 1,2,4-oxadiazole **(76**) has been found as good anticancer compound against several breast and colorectal cancer cell lines as reported by Zhang *et al*. Moreover, compound **77** has been found to have in vivo activity in a MX-1 tumor model as shown in the Table 15 [31].

1,2,3-Oxadiazole

In contrast to other oxadiazoles, 1,2,3-oxadiazole ring system is unstable. It isomerizes to formyldiazomethane [32, 33]. That's why, it is least studied for its biological activities.

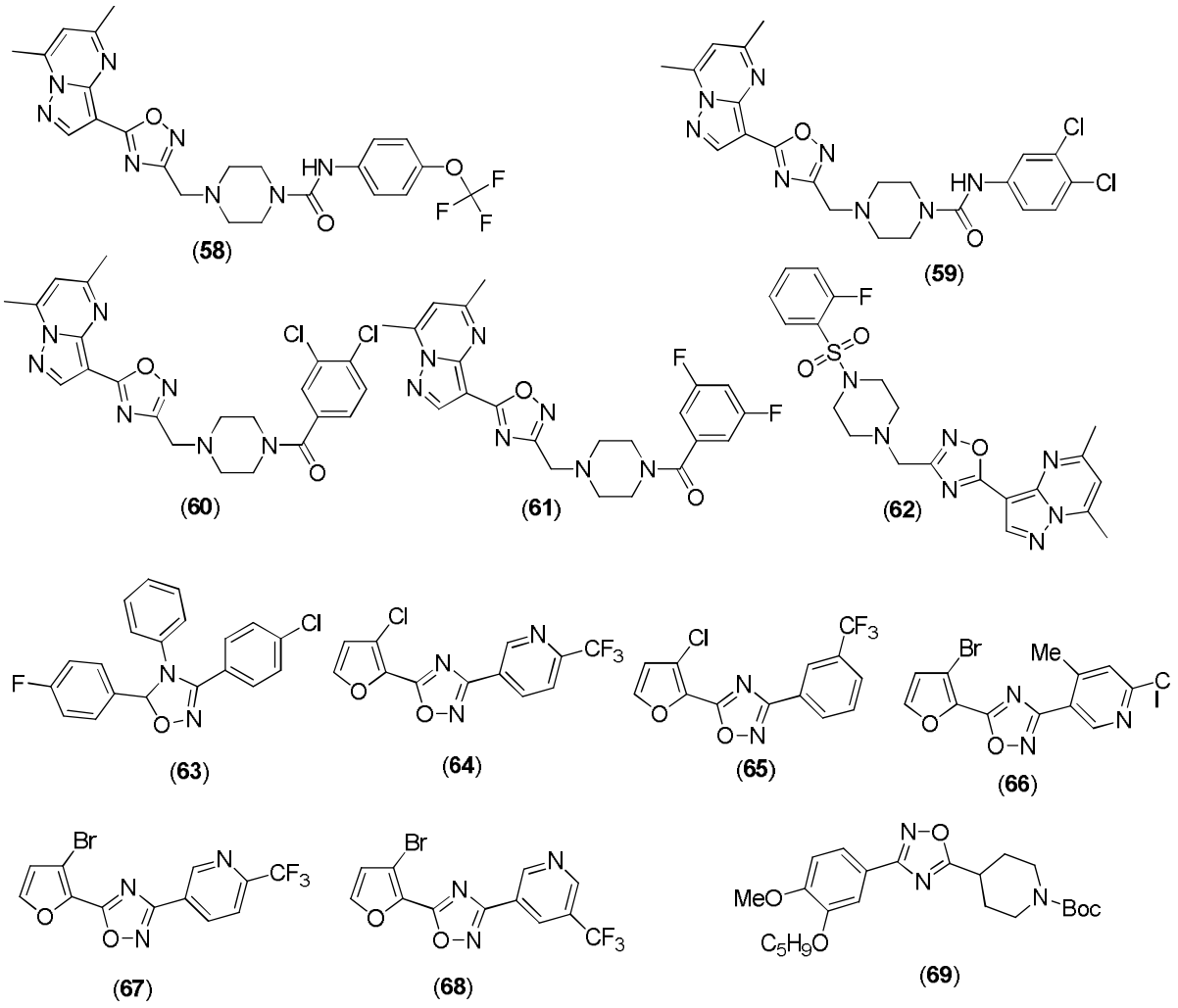

Figure 5: 1,2,4-Oxadiazoles (55-69) exhibiting potent anticancer activity

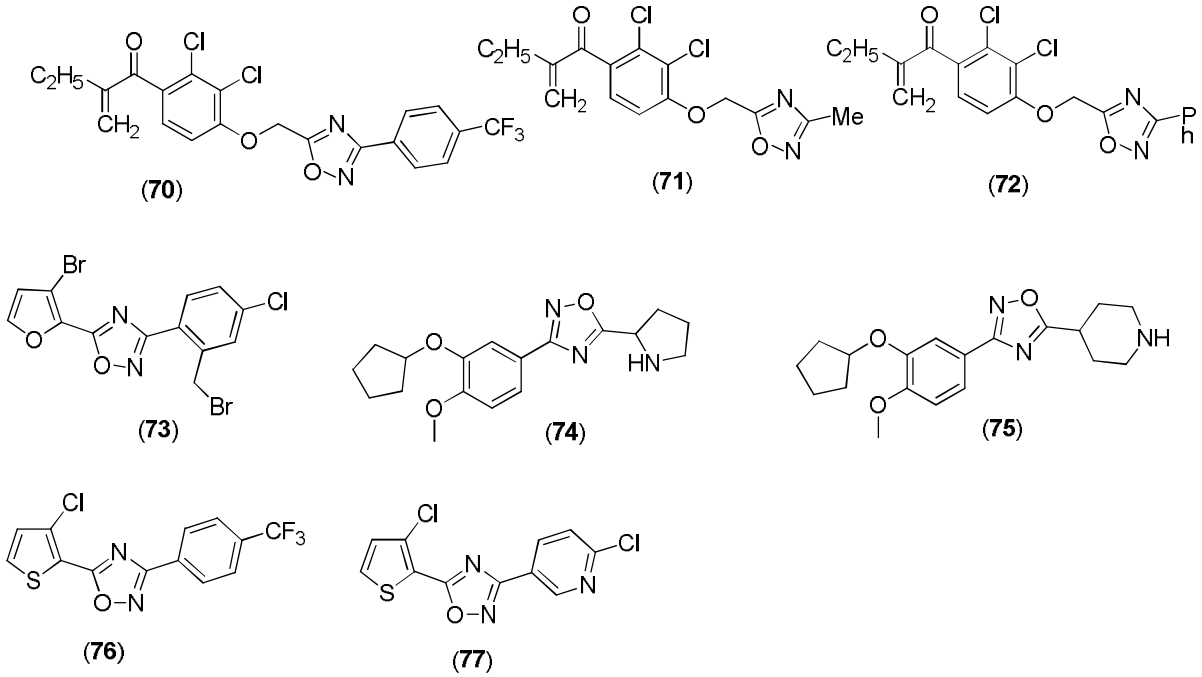

Figure 6: 1,2,4-Oxadiazoles (70-77) exhibiting potent anticancer activity

Table 12: 3-Aryl-5-aryl-1,2,4-oxadiazoles (**64-68**) as anticancer agents

Compound	EC_{50} (µM)
64	0.36
65	1.33
66	1.21
67	0.55
68	0.55

Table 13: Growth inhibition of GST P1-1 and HL-60 cells by compounds **70-72**

Compound	IC_{50} (µM) for inhibiting GST P1-1 activity	GI_{50} (µM) for inhibiting HL 60 cell growth
70	>40	1.1 ± 0.2
71	4.0 ± 0.3	2.3 ± 0.2
72	3.6 ± 0.7	1.7 ± 0.1

Table 14: Cytotoxicity profile of 3,5-disubstituted-1,2,4-oxadiazoles (IC_{50} (µM)

Compounds	PC3	DU145	LnCaP	MCF7	MDA231	HCT116	PaCa2
74	$>10^3$	242±0.1	0.043±0.04	$>10^3$	212.2±0.3	184.8 ± 0.1	19.49 ± 0.08
75	$>10^3$	0.057±0.07	0.010±0.02	3.88±0.3	0.37±0.08	1.54 ± 0.03	0.54 ± 0.03

Table 15: Cell Growth Inhibition Activity of 3-Aryl-5-aryl-1,2,4-oxadiazoles (GI_{50}, µM)

Compounds	T47D	DLD1	H1299
76	0.22 ± 0.05	0.77 ± 0.29	>10
77	0.20 ± 0.02	0.80 ± 0.11	>10

CONCLUSION

We have summed up recent literature dealing with anticancer behavior of oxadiazole ring system. Keeping in view the focus of article, we have mentioned only the potent anticancer compounds of the family. The data presented in this article is collected from recent publications in well reputed international journals of medicinal and pharmaceutical chemistry. The structural features could be interesting for medicinal chemists in devising anticancer drugs.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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